```
=> d his

     (FILE 'HOME' ENTERED AT 13:03:42 ON 22 MAR 2002)

     FILE 'REGISTRY' ENTERED AT 13:04:03 ON 22 MAR 2002
                E THALIDOMIDE/CN
L1              1 S E3
L2              5 S E3-E7
L3                STRUCTURE UPLOADED
L4             50 S L3

     FILE 'CAPLUS, USPATFULL, WPIDS, MEDLINE, DRUGU, BIOSIS' ENTERED AT
     13:08:34 ON 22 MAR 2002
L5           5637 S L1
L6           5637 S L2
L7             69 S L4
L8          57374 S ANGIOGENESIS
L9          17436 S ANGIOGENESIS###(5A)INHIBITOR##
L10             1 S L9 AND L7
L11           286 S L9 AND L6
L12        283759 S ANTIINFLAMMATOR#### OR ANTI-INFLAMMATOR#### OR ANTI INFLAMMAT
L13          1852 S L9 AND L12
L14             1 S L13 AND L7
L15            33 S L13 AND L6
L16            28 DUP REMOVE L15 (5 DUPLICATES REMOVED)

=> s (angiogenesis(5a)inhibit####)(8a)(antiinflammator#### or anti-inflammator####
or anti inflammator####)
L17           114 (ANGIOGENESIS(5A) INHIBIT####)(8A)(ANTIINFLAMMATOR#### OR ANTI-I
                  NFLAMMATOR#### OR ANTI INFLAMMATOR####)

=> s l17 and l7
L18             0 L17 AND L7

=> s l17 and l6
L19             6 L17 AND L6

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20             4 DUP REMOVE L19 (2 DUPLICATES REMOVED)

=> d l20 1-4 bib,ab

L20  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2002 ACS         DUPLICATE 1
AN   2001:318260  CAPLUS
DN   135:251525
TI   Differential effects of thalidomide on angiogenesis and tumor growth in
     mice
AU   Belo, Andrezza V.; Ferreira, Monica A. N. D.; Bosco, Adriana A.; Machado,
     Rosangela D. P.; Andrade, Silvia P.
CS   Departments of Physiology and Biophysics, Federal University of Minas
     Gerais, Belo Horizonte, Brazil
SO   Inflammation (New York, NY, United States) (2001), 25(2), 91-96
     CODEN: INFLD4; ISSN: 0360-3997
PB   Kluwer Academic/Plenum Publishers
DT   Journal
LA   English
AB   Thalidomide, clin. used as an antiinflammatory and antitumoral
     drug, inhibited sponge-induced angiogenesis when
     administered systemically (100 mg/kg-1) in mice.  However, it failed to
     inhibit solid Ehrlich tumor in the same mouse strain.  We have used
     functional, biochem. and histol. parameters to assess neovascularization
     and fibrovascular tissue infiltration of the mice sponge granuloma.  The
```

neovascularization growth as detected by development of blood flow and Hb content extd. from the implants showed that thalidomide inhibited fibrovascular tissue formation by 40%. The functional and biochem. parameters correlated well with the histol. study. Thalidomide had no inhibitory effect in the development of Ehrlich tumor. The detection of this selective action using the same animal strain bearing two different processes, supports the hypothesis that rather than species specificity, thalidomide is tissue specific. This approach may be used to identify the specificity of other therapeutic agents against distinct angiogenesis-dependent diseases.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 2000:53401 CAPLUS
DN 132:88759
TI Prophylactic treatment of neovascularization in macular degeneration using anti-inflammatory steroids
IN Gillies, Mark Cedric; Penfold, Philip Leslie; Billson, Francis Alfred
PA The University of Sydney, Australia
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002564	A1	20000120	WO 1999-AU565	19990712
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9947632	A1	20000201	AU 1999-47632	19990712
	EP 1104302	A1	20010606	EP 1999-930939	19990712
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2001000114	A	20010222	NO 2001-114	20010108
PRAI	AU 1998-4607	A	19980710		
	AU 1998-5847	A	19980911		
	WO 1999-AU565	W	19990712		

AB This invention relates to the prophylaxis of choroidal neovascularization in macular degeneration by the introduction of a suitable anti-inflammatory agent into the vitreous. In particular, it relates to the prophylaxis of neovascularization with an anti-inflammatory steroid, such as an 11-substituted 16.alpha.,17.alpha.-substituted methylenedioxy steroid of formula (I) wherein R1 and R2 are hydrogen or alkyl; -Ca-Cb- is -CH2-CH2-, -CH=CH-, -CH2CH(CH3)- or -CH=C(CH3)-; R3 is Me, hydroxymethyl or alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, or phenylaminoalkylenecarbonyloxymethyl; R4 + R6 and R5 + R6 is epoxy; R5 is halogen; R6 is hydroxyl, keto, or alkanoyl. More particularly, it relates to prophylaxis with triamcinolone acetonide.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:341075 BIOSIS
DN PREV200000341075
TI Thalidomide: Current and potential clinical applications.
AU Calabrese, Leonard (1); Fleischer, Alan B., Jr.

CS (1) Department of Rheumatic and Immunologic Disease, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH, 44195 USA
SO American Journal of Medicine, (April 15, 2000) Vol. 108, No. 6, pp. 487-495. print.
ISSN: 0002-9343.
DT General Review
LA English
SL English
AB More than three decades after its withdrawal from the world marketplace, thalidomide is attracting growing interest because of its reported immunomodulatory and anti-inflammatory properties. Current evidence indicates that thalidomide reduces the activity of the inflammatory cytokine tumor necrosis factor (TNF)-alpha by accelerating the degradation of its messenger RNA. Thalidomide also inhibits angiogenesis. Recently, the drug was approved for sale in the United States for the treatment of erythema nodosum leprosum, an inflammatory complication of Hansen's disease. However, it has long been used successfully in several other dermatologic disorders, including aphthous stomatitis, Behcet's syndrome, chronic cutaneous systemic lupus erythematosus, and graft-versus-host disease, the apparent shared characteristic of which is immune dysregulation. Many recent studies have evaluated thalidomide in patients with human immunodeficiency virus (HIV) infection; the drug is efficacious against oral aphthous ulcers, HIV-associated wasting syndrome, HIV-related diarrhea, and Kaposi's sarcoma. To prevent teratogenicity, a comprehensive program has been established to control access to the drug, including registration of prescribing physicians, dispensing pharmacies, and patients; mandatory informed consent and education procedures; and limitation of the quantity of drug dispensed. Clinical and, in some patients, electrophysiologic monitoring for peripheral neuropathy is indicated with thalidomide therapy. Other adverse effects include sedation and constipation. With appropriate safeguards, thalidomide may benefit patients with a broad variety of disorders for which existing treatments are inadequate.

L20 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 1998:341491 CAPLUS
DN 129:12742
TI Methods and compositions using thalidomide or other **angiogenesis -inhibitory** compound and **anti-inflammatory** agent for **inhibition** of **angiogenesis**
IN D'Amato, Robert J.
PA Children's Medical Center, USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9819649	A2	19980514	WO 1997-US20116	19971104
	WO 9819649	A3	19980625		
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9851973	A1	19980529	AU 1998-51973	19971104
	EP 963200	A2	19991215	EP 1997-946884	19971104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1996-28708P	P	19961105		

US 1997-963058 A 19971103
WO 1997-US20116 W 19971104

OS MARPAT 129:12742

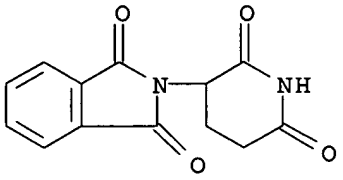
AB A group of compds. that effectively inhibit angiogenesis is provided. More specifically, thalidomide and various related compds.,e.g. thalidomide precursors, analogs, metabolites and hydrolysis products, have been shown to inhibit angiogenesis and to treat disease states resulting from angiogenesis. Addnl., **antiinflammatory** drugs, such as steroids and NSAIDs can **inhibit angiogenesis**-dependent diseases either alone or in combination with thalidomide and related compds. Importantly, these compds. can be administered orally.

```
=> e thalidomide/cn
E1            1     THALIDICINE/CN
E2            1     THALIDINE/CN
E3            1 --> THALIDOMIDE/CN
E4            1     THALIDOMIDE-ASPIRIN MIXT./CN
E5            1     THALIDOMIDE-INDOMETHACIN MIXT./CN
E6            1     THALIDOMIDE-PREDNISOLONE MIXT./CN
E7            1     THALIDOMIDE-PREDNISONE MIXT./CN
E8            1     THALIDOXINE/CN
E9            1     THALIDOXINE ACETATE/CN
E10           1     THALIFABATINE/CN
E11           1     THALIFABERIDINE/CN
E12           1     THALIFABERINE/CN

=> s e3
L1            1 THALIDOMIDE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   50-35-1  REGISTRY
CN   1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   Phthalimide, N-(2,6-dioxo-3-piperidyl)- (6CI, 7CI, 8CI)
OTHER NAMES:
CN   (.+-.)-Thalidomide
CN   .alpha.-(N-Phthalimido)glutarimide
CN   .alpha.-N-Phthalylglutaramide
CN   .alpha.-Phthalimidoglutarimide
CN   1,3-Dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline
CN   3-Phthalimidoglutarimide
CN   Celgene
CN   Contergan
CN   Distaval
CN   K 17
CN   Kevadon
CN   N-(2,6-Dioxo-3-piperidyl)phthalimide
CN   N-Phthaloylglutamimide
CN   Quetimid
CN   Sedoval
CN   Softenil
CN   Softenon
CN   Talimol
CN   Thalidomide
CN   Thalomid
FS   3D CONCORD
DR   14088-68-7, 731-40-8
MF   C13 H10 N2 O4
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS,
       CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
       DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, HODOC*, HSDB*, IPA,
       MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO,
       SYNTHLINE, TOXCENTER, USAN, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

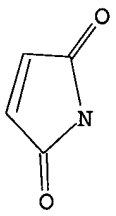
785 REFERENCES IN FILE CA (1967 TO DATE)
44 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
786 REFERENCES IN FILE CAPLUS (1967 TO DATE)
15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

```
=> s e3-e7
             1 THALIDOMIDE/CN
             1 "THALIDOMIDE-ASPIRIN MIXT."/CN
             1 "THALIDOMIDE-INDOMETHACIN MIXT."/CN
             1 "THALIDOMIDE-PREDNISOLONE MIXT."/CN
             1 "THALIDOMIDE-PREDNISONE MIXT."/CN
L2           5 (THALIDOMIDE/CN OR "THALIDOMIDE-ASPIRIN MIXT."/CN OR "THALIDOMID
               E-INDOMETHACIN MIXT."/CN OR "THALIDOMIDE-PREDNISOLONE MIXT."/CN
               OR "THALIDOMIDE-PREDNISONE MIXT."/CN)

=>
Uploading 09287377.str

L3      STRUCTURE UPLOADED

=> d l3
L3 HAS NO ANSWERS
L3              STR
```



Structure attributes must be viewed using STN Express query preparation.

```
=> s l3
SAMPLE SEARCH INITIATED 13:07:18 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  10774 TO ITERATE

  9.3% PROCESSED    1000 ITERATIONS                          50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       209270 TO   221690
PROJECTED ANSWERS:          127856 TO   137614

L4           50 SEA SSS SAM L3
```

```
=> file caplus, uspatfull, wpids, toxlit, medline, drugu, biosis
'TOXLIT' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):toxline
'TOXLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      28.14      28.29

FILE 'CAPLUS' ENTERED AT 13:08:34 ON 22 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 13:08:34 ON 22 MAR 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 13:08:34 ON 22 MAR 2002
COPYRIGHT (C) 2002 DERWENT INFORMATION LTD

FILE 'MEDLINE' ENTERED AT 13:08:34 ON 22 MAR 2002

FILE 'DRUGU' ENTERED AT 13:08:34 ON 22 MAR 2002
COPYRIGHT (C) 2002 DERWENT INFORMATION LTD

FILE 'BIOSIS' ENTERED AT 13:08:34 ON 22 MAR 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

=> d his

     (FILE 'HOME' ENTERED AT 13:03:42 ON 22 MAR 2002)

     FILE 'REGISTRY' ENTERED AT 13:04:03 ON 22 MAR 2002
                E THALIDOMIDE/CN
L1              1 S E3
L2              5 S E3-E7
L3                STRUCTURE UPLOADED
L4             50 S L3

     FILE 'CAPLUS, USPATFULL, WPIDS, MEDLINE, DRUGU, BIOSIS' ENTERED AT
     13:08:34 ON 22 MAR 2002

=> s l1
L5         5637 L1

=> s l2
L6         5637 L2

=> s l4
SAMPLE SEARCH INITIATED 13:09:09 FILE 'WPIDS'
SAMPLE SCREEN SEARCH COMPLETED -     218 TO ITERATE

100.0% PROCESSED     218 ITERATIONS                              50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.02
```

```
FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          1739 TO     2621
PROJECTED ANSWERS:             1003 TO     1697

L7          69 L4

=> s l3
SUBSTANCE QUERIES NOT VALID IN THIS FILE
SUBSTANCE QUERIES NOT VALID IN THIS FILE
SAMPLE SEARCH INITIATED 13:09:22 FILE 'WPIDS'
SAMPLE SCREEN SEARCH COMPLETED -    218 TO ITERATE

100.0% PROCESSED     218 ITERATIONS                          50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          1739 TO     2621
PROJECTED ANSWERS:             1003 TO     1697

SUBSTANCE QUERIES NOT VALID IN THIS FILE
FULL SEARCH INITIATED 13:09:24 FILE 'DRUGU'
FULL SCREEN SEARCH COMPLETED -    757 TO ITERATE

100.0% PROCESSED     757 ITERATIONS                         407 ANSWERS
SEARCH TIME: 00.00.05

SUBSTANCE QUERIES NOT VALID IN THIS FILE
The logic expression entered contains L#s or saved query names which
correspond to structures built by the STRUCTURE command or to screen
sets.  These must be searched in a substance file such as the REGISTRY
file.  In some files you may use a Registry Number answer set from a
structure search as a search term or profile in some bibliographic
file containing Registry Numbers, e.g.  the CA file.  For an
explanation, enter "HELP CROSSOVER" at an arrow prompt (=>).

=> d his

     (FILE 'HOME' ENTERED AT 13:03:42 ON 22 MAR 2002)

     FILE 'REGISTRY' ENTERED AT 13:04:03 ON 22 MAR 2002
                E THALIDOMIDE/CN
L1            1 S E3
L2            5 S E3-E7
L3              STRUCTURE UPLOADED
L4           50 S L3

     FILE 'CAPLUS, USPATFULL, WPIDS, MEDLINE, DRUGU, BIOSIS' ENTERED AT
     13:08:34 ON 22 MAR 2002
L5         5637 S L1
L6         5637 S L2
L7           69 S L4

=> s angiogenesis
L8        57374 ANGIOGENESIS

=> s angiogenesis###(5a)inhibitor##
L9        17436 ANGIOGENESIS###(5A) INHIBITOR##

=> s l9 and l7
L10           1 L9 AND L7
```

```
=> s l9 and l6
L11        286 L9 AND L6

=> s antiinflammator#### or anti-inflammator#### or anti inflammator####
L12     283759 ANTIINFLAMMATOR#### OR ANTI-INFLAMMATOR#### OR ANTI INFLAMMATOR#
               ###

=> s l9 and l12
L13       1852 L9 AND L12

=> s l13 and l7
L14          1 L13 AND L7

=> s l13 and l6
L15         33 L13 AND L6

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16          28 DUP REMOVE L15 (5 DUPLICATES REMOVED)

=> d l16 1-28 bib,ab

L16  ANSWER 1 OF 28  USPATFULL
AN     2002:37907  USPATFULL
TI     Inhibition of cyclooxygenase-2activity
IN     Dannenberg, Andrew J., New York, NY, UNITED STATES
       Muller, George, Bridgewater, NJ, UNITED STATES
PI     US 2002022627      A1   20020221
AI     US 2001-823057     A1   20010330 (9)
PRAI   US 2000-193981P     20000331 (60)
DT     Utility
FS     APPLICATION
LREP   MATHEWS, COLLINS, SHEPHERD & GOULD, P.A., 100 THANET CIRCLE, SUITE 306,
       PRINCETON, NJ, 08540-3674
CLMN   Number of Claims: 2
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 275
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     The present invention provides new methods for inhibiting the activity
       of the enzyme cycloxygenase-2 (or COX-2). Inhibitors of COX-2 are know
       to be useful anti-inflammatory, analgesic and
       anti-angiogenic agents. The compounds in the present case are
       heterocyclic substituted 4-aminoglutarimides. Methods of using the
       compounds to inhibit prostaglandin synthesis are claimed.

L16  ANSWER 2 OF 28  USPATFULL
AN     2001:185309  USPATFULL
TI     Tyrosine kinase inhibitors
IN     Fraley, Mark E., North Wales, PA, United States
       Arrington, Kenneth L., Elkins Park, PA, United States
       Bilodeau, Mark T., Lansdale, PA, United States
       Hartman, George D., Lansdale, PA, United States
       Hoffman, William F., Lansdale, PA, United States
       Kim, Yuntae, Harleysville, PA, United States
       Hungate, Randall W., Newbury Park, CA, United States
PA     Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI     US 6306874         B1   20011023
AI     US 2000-690598          20001017 (9)
PRAI   US 1999-160356P     19991019 (60)
DT     Utility
FS     GRANTED
EXNAM  Primary Examiner: Shah, Mukund J.; Assistant Examiner: Truong, Tamthom
```

N.
LREP Garcia-Rivas, J. Antonio, Daniel, Mark R.
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3068
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals.

L16 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 2001:705991 CAPLUS
DN 136:47943
TI Thalidomide is distributed into human semen after oral dosing
AU Teo, Steve K.; Harden, Jill L.; Burke, Alison B.; Noormohamed, Faruq H.; Youle, Mike; Johnson, Margaret A.; Peters, Barry S.; Stirling, David I.; Thomas, Steve D.
CS Celgene Corporation, Warren, NJ, 07059, USA
SO Drug Metabolism and Disposition (2001), 29(10), 1355-1357
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB As part of a double-blind placebo-controlled study of the effect of thalidomide on body wt. and the viral load of human immunodeficiency virus-seropos. patients, blood plasma and semen samples were analyzed for the presence of thalidomide. Patients were orally dosed with 100 mg of thalidomide/day for 8 wk. Blood samples were obtained at baseline and weeks 4, 8, and 12, and semen was obtained at baseline and weeks 4 and 8. Samples were extd. with solid-phase cartridges and analyzed by liq. chromatog./tandem mass spectrometry using atm. pressure chem. ionization in the neg. ion mode. Two of 4 patients taking thalidomide were able to provide semen samples. Both had detectable levels of thalidomide in their plasma (10-350 ng/mL) and semen (10-250 ng/g) at weeks 4 and 8. There was an apparent correlation between plasma and semen levels. Semen levels could be significantly greater for therapeutic doses of more than 100 mg/day. Since the threshold dose for birth defects and thalidomide exposure is not known, male patients are advised to use barrier contraception.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2002-03184 DRUGU P
TI The anti-angiogenic agents angiostatin and thalidomide inhibit cervical cancer growth in a murine model.
AU Stanford Downs L; Ramakrishnan S
CS Univ.Minnesota
LO Minneapolis, Minn., USA
SO Proc.Am.Assoc.Cancer Res. (42, 92 Meet., 584, 2001) ISSN: 0197-016X
AV The University of Minnesota, Minneapolis, MN, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The effects of antiangiogenic agents on the growth of human papilloma virus positive squamous-cell cervical cancer cells were studied. Murine angiostatin and thalidomide both inhibited the growth of tumor xenografts in nude mice. Angiostatin but not thalidomide inhibited basic fibroblast

growth factor stimulated proliferation of human umbilical vein endothelial cells in-vitro. The results suggest that antiangiogenic drugs may be clinically useful in squamous-cell cervical carcinoma. (conference abstract: 92nd Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, 2001). (No EX).

L16 ANSWER 5 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-33250 DRUGU P
TI A difference between the rat and mouse in the pharmacokinetic interaction of 5,6-dimethylxanthenone-4-acetic acid with thalidomide.
AU Zhou S; Kestell P; Tingle M D; Ching L M; Paxton J W
CS Univ.Auckland
LO Auckland, N.Z.
SO Cancer Chemother.Pharmacol. (47, No. 6, 541-44, 2001) 2 Tab. 31 Ref.
CODEN: CCPHDZ ISSN: 0344-5704
AV Department of Pharmacology and Clinical Pharmacology, The University of Auckland School of Medicine, Private Bag 92019, Auckland, New Zealand. (J.W.P.; e-mail: j.paxton@auckland.ac.nz).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB No significant alteration in the plasma concentration profile for i.v. 5,6-dimethylxanthenone-4-acetic acid (DMXAA, NSC-640488) was seen following i.p. L-thalidomide (L-Thal) pretreatment in rats. However, when rats were pretreated with i.p. diclofenac or i.p. cyproheptadine (both Sigma-Aldrich), the plasma AUC and half-life of DMXAA were significantly increased. In rat liver microsomes, diclofenac inhibited glucuronidation and 6-methylhydroxylation of DMXAA, while cyproheptadine inhibited glucuronidation, but not 6-methylhydroxylation. L-Thal resulted in negligible inhibition of DMXAA metabolism in rat liver microsomes. In contrast to previous murine studies, co-administration of L-Thal in rats did not alter the pharmacokinetics of DMXAA.

L16 ANSWER 6 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2002-02680 DRUGU P T S
TI Clinical pharmacology of thalidomide.
AU Eriksson T; Bjorkman S; Hoglund P
CS Univ.Lund; Univ.Malmo
LO Lund; Malmo, Swed.
SO Eur.J.Clin.Pharmacol. (57, No. 5, 365-76, 2001) 2 Fig. 5 Tab. 87 Ref.
CODEN: EJCPAS ISSN: 0031-6970
AV Hospital Pharmacy, University Hospital, 221 85 Lund, Sweden. (e-mail: tommy.eriksson@apoteket.se).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The clinical pharmacology of thalidomide (THAL) is reviewed with emphasis on the chemistry and chirality, pharmacokinetics, pharmacodynamics, clinical use, adverse effects and dose/administration. (S)-THAL was introduced as a sedative drug in the late 1950s, but in 1961, it was withdrawn due to teratogenicity and neuropathy. However, there is now a growing clinical interest in THAL due to its unique **antiinflammatory**, antiangiogenic and immunomodulatory effects. Inter-individual variability in distribution and elimination are low. Rational use of THAL is problematic due to lack of basic knowledge of its mechanism of action, effects of the separate enantiomers and metabolites and dose- and concentration-effect relationships.

L16 ANSWER 7 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-24865 DRUGU M P
TI In vitro and in vivo kinetic interactions of the antitumour agent 5,6-dimethylxanthenone-4-acetic acid with thalidomide and diclofenac.

AU Zhou S; Paxton J W; Kestell P; Tingle M D; Ching L M
LO Auckland, N.Z.
SO Cancer Chemother.Pharmacol. (47, No. 4, 319-26, 2001) 2 Fig. 3 Tab. 37 Ref.
CODEN: CCPHDZ ISSN: 0344-5704
AV Department of Pharmacology and Clinical Pharmacology, The University of Auckland School of Medicine, Private Bag 92019, Auckland, New Zealand. (J.W.P.). (e-mail: j.paxton@auckland.ac.nz).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB Pretreatment with i.p. diclofenac (DIC, Sigma-Aldrich) increased the AUC of 5,6-dimethylxanthenone-4-acetic acid (DM) whereas L-thalidomide (L-TA) produced only little or no increase in AUC of DM in a controlled study of mice. In vitro, DIC competitively inhibited DM glucuronidation and 6-methylhydroxylation (6-MET) in male and female mice and human microsomes. L-TA dose-dependently reduced 6-MET in all mice and human microsomes. L-TA and DIC increased the plasma AUC and elimination half-life of DM. DIC and L-TA had no effect on the in vitro plasma protein binding of DM in mouse or human plasma. Results show that a model based on the direct inhibition of metabolism appears to be appropriate for the prediction of DIC-DM pharmacokinetic interactions in mice and humans in vivo, but is inappropriate for the prediction of L-TA-DM pharmacokinetic interactions.

L16 ANSWER 8 OF 28 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
AN 2001:318260 CAPLUS
DN 135:251525
TI Differential effects of thalidomide on angiogenesis and tumor growth in mice
AU Belo, Andrezza V.; Ferreira, Monica A. N. D.; Bosco, Adriana A.; Machado, Rosangela D. P.; Andrade, Silvia P.
CS Departments of Physiology and Biophysics, Federal University of Minas Gerais, Belo Horizonte, Brazil
SO Inflammation (New York, NY, United States) (2001), 25(2), 91-96
CODEN: INFLD4; ISSN: 0360-3997
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB Thalidomide, clin. used as an **antiinflammatory** and antitumoral drug, inhibited sponge-induced angiogenesis when administered systemically (100 mg/kg-1) in mice. However, it failed to inhibit solid Ehrlich tumor in the same mouse strain. We have used functional, biochem. and histol. parameters to assess neovascularization and fibrovascular tissue infiltration of the mice sponge granuloma. The neovascularization growth as detected by development of blood flow and Hb content extd. from the implants showed that thalidomide inhibited fibrovascular tissue formation by 40%. The functional and biochem. parameters correlated well with the histol. study. Thalidomide had no inhibitory effect in the development of Ehrlich tumor. The detection of this selective action using the same animal strain bearing two different processes, supports the hypothesis that rather than species specificity, thalidomide is tissue specific. This approach may be used to identify the specificity of other therapeutic agents against distinct angiogenesis-dependent diseases.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
AN 2001:161292 CAPLUS
DN 135:204591
TI Thalomid (thalidomide) capsules: A review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing

AU Clark, Todd E.; Edom, Norma; Larson, Janice; Lindsey, Laura J.
CS Drug Safety Department, Celgene Corporation, Warren, NJ, USA
SO Drug Safety (2001), 24(2), 87-117
CODEN: DRSAEA; ISSN: 0114-5916
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review with 142 refs. The sedative/hypnotic thalidomide was withdrawn from the worldwide market nearly 40 yr ago, because of its teratogenic and neurotoxic effects. Thalidomide was later found to very effectively suppress erythema nodosum leprosum (ENL). The US Food and Drug Administration (FDA) has approved Thalomid (thalidomide) capsules for the acute treatment of the cutaneous manifestations of moderate to severe ENL. Thalidomide is currently under investigation for the treatment of a wide variety of diseases, including conditions thought to have an inflammatory or immune basis, malignancies and complications of infection with HIV. Interest in the potential **anti-inflammatory**, immunomodulatory and anti-angiogenic effects of thalidomide has resulted in off-label use of prescription thalidomide. During the first 18 mo of spontaneous postmarketing adverse event surveillance for Thalomid, 1210 spontaneous postmarketing adverse event reports were received for patients treated with prescription thalidomide for all therapeutic indications, including off-label use. The most common adverse events spontaneously reported would have been expected on the basis of the current Thalomid labeling/product information. The current labeling/product information reflects what was known about the risks assocd. with thalidomide therapy in limited patient populations at the time of the approval of Thalomid. With the postmarketing use of thalidomide in populations other than patients with ENL, it becomes increasingly important to identify patient groups that may be particularly susceptible to specific adverse drug effects and to identify conditions under which specific adverse events may be more likely to occur. Oncol. patients may represent a patient population with increased susceptibility to thalidomide-assocd. adverse effects, including thromboembolic events. Consideration of the spontaneous postmarketing safety surveillance data may help to identify and characterize factors assocd. with increased risk in this and other patient groups. Serious unexpected adverse events reported with sufficient frequency to signal previously undetected product-event assocns. for which there may potentially be plausible evidence to suggest a causal relationship have included seizures and Stevens-Johnson syndrome. The potential effects of thalidomide on wound healing are also being closely monitored. Premarketing human clin. trials of drug products are inherently limited in their ability to detect adverse events. Broader postmarketing experience with thalidomide in more varied patient populations and more experience in the setting of long term thalidomide use will increase our ability to detect rare adverse events and to identify signals that may need to be evaluated in more controlled settings.
RE.CNT 142 THERE ARE 142 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-47513 DRUGU P
TI Thalidomide inhibits inflammatory and angiogenic activation of human intestinal microvascular endothelial cells (HIMEC).
AU Stein D J; Rafiee P; Taras A; Lamirand T H; Fisher P J; Ogawa H; Telford G L; Otterson M F; Johnson C P; Binion D G
CS Wisconsin-Med.Coll.
LO Milwaukee, Wis., USA
SO Gastroenterology (120, No. 5, Suppl. 1, A278, 2001)
CODEN: GASTAB ISSN: 0016-5085
AV Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A.
LA English
DT Journal

FA AB; LA; CT
FS Literature
AB The effect of thalidomide (Celgene) on primary cultures of human intestinal microvascular endothelial cells (HIMEC) activation, leukocyte interaction and angiogenesis was investigated in-vitro. Thalidomide potently inhibited HIMEC inflammatory and angiogenic activation. The results suggest a therapeutic role for thalidomide in the treatment of Crohn's disease. (conference abstract: 102nd Annual Meeting of the American Gastroenterological Association, Atlanta, Georgia, USA, 2001).

L16 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 2000:456819 CAPLUS
DN 133:84238
TI 3-heteroarylidenyl-2-indolinone compounds for modulating protein kinase activity and for use in cancer chemotherapy
IN Langecker, Peter J.; Shawver, Laura Kay; Tang, Peng Cho; Sun, Li
PA Sugen, Inc., USA
SO PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000038519	A1	20000706	WO 1999-US31232	19991230
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 9916735	A	20010925	BR 1999-16735	19991230
EP 1139754	A1	20011010	EP 1999-966725	19991230
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2001049287	A1	20010712	WO 2000-US18058	20000630
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI	US 1998-114313P	P	19981231
	US 1999-476232	A	19991230
	WO 1999-US31232	W	19991230
	US 2000-569545	A	20000512

OS MARPAT 133:84238
AB 3-Heteroarylidenyl-2-indolinone compds. are provided that modulate the enzymic activity of protein kinases and therefore are expected to be useful in the prevention and treatment of protein kinase-related cellular disorders, e.g. cancer. Furthermore, these compds. are expected to enhance the efficacy of other chemotherapeutic agents, in particular, fluorinated pyrimidines, in the treatment of cancer.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 2000:53401 CAPLUS
DN 132:88759

TI Prophylactic treatment of neovascularization in macular degeneration using **anti-inflammatory** steroids
IN Gillies, Mark Cedric; Penfold, Philip Leslie; Billson, Francis Alfred
PA The University of Sydney, Australia
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002564	A1	20000120	WO 1999-AU565	19990712
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9947632	A1	20000201	AU 1999-47632	19990712
	EP 1104302	A1	20010606	EP 1999-930939	19990712
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2001000114	A	20010222	NO 2001-114	20010108
PRAI	AU 1998-4607	A	19980710		
	AU 1998-5847	A	19980911		
	WO 1999-AU565	W	19990712		

AB This invention relates to the prophylaxis of choroidal neovascularization in macular degeneration by the introduction of a suitable **anti-inflammatory** agent into the vitreous. In particular, it relates to the prophylaxis of neovascularization with an **anti-inflammatory** steroid, such as an 11-substituted 16.alpha.,17.alpha.-substituted methylenedioxy steroid of formula (I) wherein R1 and R2 are hydrogen or alkyl; -Ca-Cb- is -CH2-CH2-, -CH=CH-, -CH2CH(CH3)- or -CH=C(CH3)-; R3 is Me, hydroxymethyl or alkylcarbonyloxymethyl, methylaminoalkylenecarbonyloxymethyl, or phenylaminoalkylenecarbonyloxymethyl; R4 + R6 and R5 + R6 is epoxy; R5 is halogen; R6 is hydroxyl, keto, or alkanoyl. More particularly, it relates to prophylaxis with triamcinolone acetonide.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 13 OF 28 MEDLINE
AN 2001068861 MEDLINE
DN 20386262 PubMed ID: 10933131
TI Intravenous formulations of the enantiomers of thalidomide: pharmacokinetic and initial pharmacodynamic characterization in man.
AU Eriksson T; Bjorkman S; Roth B; Hoglund P
CS Hospital Pharmacy, Malmo University Hospital, Sweden.
SO JOURNAL OF PHARMACY AND PHARMACOLOGY, (2000 Jul) 52 (7) 807-17.
Journal code: JNR. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010104
AB Thalidomide, a racemate, is coming into clinical use as an

immunomodulating and **antiinflammatory** drug. These effects may chiefly be exerted by S-thalidomide, but the enantiomers are interconverted in-vivo. Thalidomide is given orally, although parenteral administration would be desirable in some clinical situations. The aim of this study was to prepare solutions of the enantiomers of thalidomide for intravenous administration and to investigate their pharmacokinetics and sedative effects following infusion in man. Solubility and stability of the enantiomers in 5% glucose solution was investigated. After a dose-determination experiment in one subject, six healthy male volunteers received R- and S-thalidomide separately by 1-h infusions in a randomized double-blind cross-over study. Blood was sampled over 22h and sedative effects were recorded. Blood concentrations of the enantiomers were determined by stereospecific HPLC. A four-compartment model consisting of a two-compartment model for each enantiomer, with elimination from both compartments, connected by rate constants for chiral inversion was fitted to the concentration data, while the sedative effects were correlated with the blood concentrations of R- and S-thalidomide by means of logistic regression. The enantiomers of thalidomide were chemically stable in solution for at least a week at room temperature. The infusions were well tolerated. Sedation, which was the only observed effect, was related to the blood concentration of R-thalidomide. Inter-individual variation in the disposition of the enantiomers was modest (e.g. terminal half-lives ranged between 3.9 and 5.3h). Pharmacokinetic modelling predicted that varying the infusion time of a fixed dose of S-thalidomide between 10 min and 6h would have little influence on the maximal blood concentration of formed R-thalidomide. To our knowledge this is the first time that thalidomide has been administered intravenously.

L16 ANSWER 14 OF 28 MEDLINE DUPLICATE 3
AN 2000245091 MEDLINE
DN 20245091 PubMed ID: 10781782
TI Thalidomide: current and potential clinical applications.
AU Calabrese L; Fleischer A B
CS Department of Rheumatic and Immunologic Disease, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio, USA.
SO AMERICAN JOURNAL OF MEDICINE, (2000 Apr 15) 108 (6) 487-95. Ref: 96
Journal code: 3JU; 0267200. ISSN: 0002-9343.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200006
ED Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000616
AB More than three decades after its withdrawal from the world marketplace, thalidomide is attracting growing interest because of its reported immunomodulatory and **anti-inflammatory** properties.
Current evidence indicates that thalidomide reduces the activity of the inflammatory cytokine tumor necrosis factor (TNF)-alpha by accelerating the degradation of its messenger RNA. Thalidomide also inhibits angiogenesis. Recently, the drug was approved for sale in the United States for the treatment of erythema nodosum leprosum, an inflammatory complication of Hansen's disease. However, it has long been used successfully in several other dermatologic disorders, including aphthous stomatitis, Behcet's syndrome, chronic cutaneous systemic lupus erythematosus, and graft-versus-host disease, the apparent shared characteristic of which is immune dysregulation. Many recent studies have evaluated thalidomide in patients with human immunodeficiency virus (HIV) infection; the drug is efficacious against oral aphthous ulcers, HIV-associated wasting syndrome, HIV-related diarrhea, and Kaposi's sarcoma. To prevent teratogenicity, a comprehensive program has been

established to control access to the drug, including registration of prescribing physicians, dispensing pharmacies, and patients; mandatory informed consent and education procedures; and limitation of the quantity of drug dispensed. Clinical and, in some patients, electrophysiologic monitoring for peripheral neuropathy is indicated with thalidomide therapy. Other adverse effects include sedation and constipation. With appropriate safeguards, thalidomide may benefit patients with a broad variety of disorders for which existing treatments are inadequate.

L16 ANSWER 15 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-31947 DRUGU P V
TI Angiogenesis inhibition in cancer prevention: a quantitative angiogenesis model for efficacy testing of chemopreventive agents.
AU Sharma S; Ghoddoussi M C; Gao P; Kelloff G J; Steele V E; Kopelovich L
CS ManTech; Nat.Cancer-Inst.Rockville
LO Research Triangle Park, N.C.; Rockville, Md., USA
SO Proc.Am.Assoc.Cancer Res. (41, 91 Meet., 411, 2000) ISSN: 0197-016X
AV ManTech Environmental Technology, RTP, NC, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB A quantitative in-vivo angiogenesis inhibition assay was developed to test the efficacy of chemopreventive agents such as thalidomide (TH), aspirin (AS), piroxicam (PC), curcumin (CM), sulindac (SU), 13-cis-retinoic acid (13-cis-RA, isotretinoin), 9-cis-retinoic acid (9-cis-RA), all-trans-retinoic acid (tretinoin, TT) and 4-hydroyphenyl retinamide (4-HPR, fenretinide) using the chick chorioallantoic membrane (CAM) model and an oncogene-transfected angiogenic cell line (6 Ti ras/SV myc # 4). Angiogenesis inhibition is another desirable attribute for chemopreventive agents belonging to different chemical classes or biological activities. (conference abstract: 91st Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2000).

L16 ANSWER 16 OF 28 USPATFULL
AN 1999:1647 USPATFULL
TI Methods for inhibiting proliferation of tumor cells and tumor growth
IN Backer, Joseph M., Tenafly, NJ, United States
Bohlen, Peter, Cortland Manor, NY, United States
PA American Cyanamid Company, Madison, NJ, United States (U.S. corporation)
PI US 5856315 19990105
AI US 1998-84484 19980526
RLI Division of Ser. No. US 1994-354694, filed on 13 Dec 1994
DT Utility
FS Granted
EXNAM Primary Examiner: Sayala, Chhaya D.
LREP Nagy, Michael R.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 787
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method for inhibiting angiogenesis and proliferation of endothelial cells by administering an inhibitory amount of 7-[substituted amino]-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracycline of Formula I: ##STR1## wherein R, R.sub.2, R.sub.3, and W are as defined in the specification. The invention also relates to a method for inhibiting proliferation of tumor cells and tumor growth by administering an inhibitory amount of a compound of Formula I in combination with a chemotherapeutic agent or radiation therapy. The invention also relates to compositions containing an effective inhibitory amount of a compound of Formula I in a pharmaceutically

acceptable carrier.

L16 ANSWER 17 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1999-27327 DRUGU P
TI **Angiogenesis** activators and **inhibitors** differentially regulate caveolin-1 expression and caveolae formation in vascular endothelial cells.
AU Liu J; Razani B; Tang S; Terman B I; Ware J A; Lisanti M P
CS Albert-Einstein-Coll.Med.
LO New York, N.Y., USA
SO J.Biol.Chem. (274, No. 22, 15781-85, 1999) 5 Fig. 54 Ref.
CODEN: JBCHA3 ISSN: 0021-9258
AV Dept. of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, U.S.A. (M.P.L.). (e-mail: lisanti@aecom.yu.edu).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The effect of angiogenesis activators, vascular endothelial growth factor (VEGF, Peprotech), basic fibroblast growth factor (bFGF, Upstate-Biotechnology) and hepatocyte growth factor (HGF, Sigma-Chem.) and **angiogenesis inhibitors** angiostatin (AS, **Angiogenesis**-Res.Ind.), fumagillin (FG), 2-methoxyestradiol (ME, both Calbiochem), transforming growth factor-beta (TGF, Upstate-Biotechnol.), thalidomide (TD) and PD-98059 (PD, both Calbiochem) on caveolin-1 expression and caveolae formation in vascular endothelial ECV-304 cells was investigated in-vitro. VEGF, bFGF and HGF all down-regulated the expression of caveolin-1. AS, FG, ME, TGF, TD and PD all selectively blocked the ability of VEGF to induce the down-regulation of caveolin-1. In conclusion, down-regulation of caveolin-1 may be an important step along the pathway toward endothelial cell proliferation.

L16 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 1999:760382 CAPLUS
DN 132:73073
TI Thalidomide as an emerging immunotherapeutic agent
AU Marriott, J. B.; Muller, G.; Dalgleish, A. G.
CS Dept of Cellular and Molecular Sciences, Division of Oncology, St George's Hospital Medical School, London, UK
SO Immunol. Today (1999), 20(12), 538-540
CODEN: IMTOD8; ISSN: 0167-4919
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A review with 52 refs. Thalidomide first hit the headlines with alarming reports of birth defects after pregnant women took the drug to combat morning sickness. Now, the drug has been shown to have important immunomodulatory and **anti-inflammatory** effects that may be useful in the treatment of AIDS and cancer.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
AN 1999:68675 CAPLUS
DN 130:291172
TI Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumor growth in rabbits
AU Verheul, H. M. W.; Panigrahy, D.; Yuan, J.; D'Amato, R. J.
CS Department of Surgery, Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA
SO Br. J. Cancer (1999), 79(1), 114-118
CODEN: BJCAAI; ISSN: 0007-0920
PB Churchill Livingstone

DT Journal
LA English
AB Neovascularization facilitates tumor growth and metastasis formation. In our lab., we attempt to identify clin. available oral efficacious drugs for antiangiogenic activity. Here, we report which non-steroidal **anti-inflammatory** drugs (NSAIDs) can inhibit corneal neovascularization, induced by basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF). This antiangiogenic activity may contribute to the known effects of NSAIDs on gastric ulcers, polyps and tumors. We found that sulindac was one of the most potent antiangiogenic NSAIDs, inhibiting bFGF-induced neovascularization by 50% and VEGF-induced neovascularization by 55%. Previously, we reported that thalidomide inhibited growth factor-induced corneal neovascularization. When we combined sulindac with thalidomide, we found a significantly increased inhibition of bFGF- or VEGF-induced corneal neovascularization (by 63% or 74% resp.) compared with either agent alone ($P < 0.01$). Because of this strong antiangiogenic effect, we tested the oral combination of thalidomide and sulindac for its ability to inhibit the growth of V2 carcinoma in rabbits. Oral treatment of thalidomide or sulindac alone inhibited tumor growth by 55% and 35% resp. When given together, the growth of the V2 carcinoma was inhibited by 75%. Our results indicated that oral antiangiogenic combination therapy with thalidomide and sulindac may be a useful non-toxic treatment for cancer.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 20 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-01016 DRUGU P S
TI Phosphodiesterase inhibitors prevent NSAID enteropathy independently of effects on TNF-alpha release.
AU Reuter B K; Wallace J L
CS Univ.Calgary
LO Calgary, Alb., Can.
SO Am.J.Physiol. (277, No. 4, Pt. 1, G847-G854, 1999) 9 Fig. 39 Ref.
CODEN: AJPHAP ISSN: 0002-9513
AV Dept. of Pharmacology and Therapeutics, University of Calgary, 330 Hospital Dr. NW, Calgary, AB, Canada T2N 4N1. (J.L.W.). (e-mail: wallacej@ucalgary.ca).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The effect of various TNF-alpha inhibitors including phosphodiesterase inhibitors (pentoxifylline, theophylline and rolipram), thalidomide and anti-TNF-alpha antibodies was studied in rats with small intestinal injury induced by the NSAID p.o. diclofenac. The study showed that TNF-alpha does not appear to play a critical role in the pathogenesis of NSAID-induced small intestinal injury. The phosphodiesterase inhibitors pentoxifylline and theophylline, but not thalidomide or anti-TNF-alpha antibodies were able to protect against diclofenac induced intestinal damage. Rolipram had a protective effect at high doses.

L16 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 1998:341491 CAPLUS
DN 129:12742
TI Methods and compositions using thalidomide or other **angiogenesis -inhibitory** compound and **anti-inflammatory** agent for inhibition of angiogenesis
IN D'Amato, Robert J.
PA Children's Medical Center, USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9819649	A2	19980514	WO 1997-US20116	19971104
	WO 9819649	A3	19980625		
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9851973	A1	19980529	AU 1998-51973	19971104
	EP 963200	A2	19991215	EP 1997-946884	19971104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1996-28708P	P	19961105		
	US 1997-963058	A	19971103		
	WO 1997-US20116	W	19971104		

OS MARPAT 129:12742

AB A group of compds. that effectively inhibit angiogenesis is provided. More specifically, thalidomide and various related compds.,e.g. thalidomide precursors, analogs, metabolites and hydrolysis products, have been shown to inhibit angiogenesis and to treat disease states resulting from angiogenesis. Addnl., **antiinflammatory** drugs, such as steroids and NSAIDs can inhibit angiogenesis-dependent diseases either alone or in combination with thalidomide and related compds. Importantly, these compds. can be administered orally.

L16 ANSWER 22 OF 28 USPATFULL

AN 1998:150927 USPATFULL

TI Methods for inhibiting angiogenesis, proliferation of endothelial or tumor cells and tumor growth

IN Backer, Joseph M., Tenafly, NJ, United States
Bohlen, Peter, Cortland Manor, NY, United States

PA American Cyanamid Company, Madison, NJ, United States (U.S. corporation)

PI US 5843925 19981201

AI US 1994-354694 19941213 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Sayala, Chhaya D.

LREP Nagy, Michael R.

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 861

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a method for inhibiting angiogenesis and proliferation of endothelial cells by administering an inhibitory amount of a 7-[substituted amino]-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracycline of Formula I: ##STR1## wherein R, R.sub.2, R.sub.3, and W are as defined in the specification. The invention also relates to a method for inhibiting proliferation of tumor cells and tumor growth by administering an inhibitory amount of a compound of Formula I in combination with a chemotherapeutic agent or radiation therapy. The invention also relates to compositions containing an effective inhibitory amount of a compound of Formula I in a pharmaceutically acceptable carrier.

L16 ANSWER 23 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:170942 BIOSIS

DN PREV199800170942

TI Thalidomide reduces vascular density in granulation tissue of

subcutaneously implanted polyvinyl alcohol sponges ion guinea pigs.
AU Or, Reuven (1); Feferman, Regina; Shoshan, Shmuel
CS (1) Dep. Bone Marrow Transplantation, Hadassah Univ. Hosp., P.O. Box 12000, Jerusalem 91120 Israel
SO Experimental Hematology (Charlottesville), (March, 1998) Vol. 26, No. 3, pp. 217-221.
ISSN: 0301-472X.
DT Article
LA English
AB The efficacy of thalidomide in the treatment of erythema nodosum leprosum is a well established fact; there is also accumulating evidence of its therapeutic value in a number of other inflammatory and immune-mediated conditions. In addition, thalidomide has been shown to be an **inhibitor** of **angiogenesis** induced by basic fibroblast growth factor (bFGF). Nevertheless, its mechanism of action remains speculative. Using guinea pigs, orally administered thalidomide significantly enhanced the response of multinucleated foreign body giant cells ($p < 0.05$) in subcutaneously implanted polyvinyl alcohol sponges. Furthermore, the drug exerted a dual effect in that it reduced vascular density ($p < 0.05$), which was not abolished by recombinant human bFGF, and at the same time amplified the granulomatous response with and without bFGF ($p < 0.05$ and $p < 0.01$, respectively). The results of our experiments represent a further step toward understanding the mechanism of action of thalidomide, with implications for its potential use in wound healing and scar formation as well as in the control of tumorigenesis.

L16 ANSWER 24 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1999-04355 DRUGU P S
TI Phosphodiesterase inhibitors prevent NSAID-induced small intestinal injury: a role for tumour necrosis factor-alpha
AU Reuter B K; Wallace J L
CS Univ.Calgary
LO Calgary, Alb., Can.
SO Arch.Pharmacol. (358, No. 1, Suppl. 1, R352, 1998)
CODEN: NSAPCC ISSN: 0028-1298
AV University of Calgary, Calgary, Alberta, Canada T2N 4N1.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The effects of i.p. phosphodiesterase inhibitors (pentoxifylline, theophylline or thalidomide) were examined in a p.o. diclofenac-induced small intestine injury model in rats. Pentoxifylline and theophylline, but not thalidomide protected the rat small intestine from ulceration caused by diclofenac. All 3 compounds inhibited the increase in TNF-alpha levels caused by lipopolysaccharide. Pentoxifylline and theophylline had protection against NSAID-induced small intestine injury, but the action is not related to their ability to inhibit TNF-alpha synthesis. (conference abstract: XIIIth International Congress of Pharmacology, Munich, Germany, 1998).

L16 ANSWER 25 OF 28 USPATFULL
AN 97:68480 USPATFULL
TI Treatment of inflammatory and/or autoimmune dermatoses with thalidomide alone or in combination with other agents
IN Andrulis, Jr., Peter J., Bethesda, MD, United States
Drulak, Murray W., Gaithersburg, MD, United States
PA Andrulis Pharmaceuticals, Beltsville, MD, United States (U.S. corporation)
PI US 5654312 19970805
AI US 1995-475426 19950607 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Nutter, Nathan M.

LREP Angres, Isaac
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 925
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treatment for inflammatory and autoimmune dermatoses which comprises topical and/or systemic administration of a therapeutically-effective amount of thalidomide alone or in combination with other dermatological agents.

L16 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2002 ACS
AN 1997:593792 CAPLUS
DN 127:242709
TI Thalidomide may impede cell migration in primates by down-regulating integrin .beta.-chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis
AU Mccarty, M. F.
CS Nutrition 21, San Diego, CA, 92109, USA
SO Med. Hypotheses (1997), 49(2), 123-131
CODEN: MEHYDY; ISSN: 0306-9877
PB Churchill Livingstone
DT Journal; General Review
LA English
AB A review with 108 refs. A growing no. of human inflammatory disorders are reported to respond to treatment with thalidomide, and recently this drug has been shown to inhibit angiogenesis in the rabbit, in doses which can elicit teratogenicity in this species. Studies in marmosets and humans indicate that thalidomide, and a teratogenic analog, decrease the expression of .beta. integrin subunits, most notably .beta.3 and the .beta.2 produced by leukocytes. Since integrins are crucial for cell-matrix interactions, and the .beta.2 integrins of leukocytes mediate adhesion to endothelium, it is reasonable to postulate that thalidomide inhibits cell migration in susceptible species, and that this accounts for its **anti-inflammatory**, anti-angiogenic, and teratogenic activity. This perspective suggests that thalidomide will show utility in the prevention or treatment of a wide range of disorders, including solid tumors, proliferative retinopathies, many inflammatory diseases, neointimal hyperplasia, and osteoporosis. It is likely that dietary fish oil - as well as selective inhibitors of urokinase, when and if they become clin. available - will complement the efficacy of thalidomide in most if not all of these applications.

L16 ANSWER 27 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:224768 BIOSIS
DN PREV199698780897
TI New uses of thalidomide.
AU Anonymous
SO Medical Letter (New Rochelle), (1996) Vol. 38, No. 968, pp. 15-16.
ISSN: 0025-732X.
DT Article
LA English
AB Investigational drug status has been granted to thalidomide in the US for clinical trials in erythema nodosum leprosum, aphthous ulcers in patients with and without HIV (human immunodeficiency virus) infection, Behcet's disease, chronic graft versus host disease, inflammatory dermatoses and AIDS (acquired immune deficiency syndrome) wasting. The immunomodulator has several serious side effects, the most common being teratogenicity. The drug is available from Celgene, Andrulis, and the FDA.

L16 ANSWER 28 OF 28 DRUGU COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1995-31063 DRUGU P
TI Thalidomide analogs suppress rat collagen arthritis.

AU Oliver S J; Cheng T P; Banquerigo L; Brahn E
CS Univ.California
LO Los Angeles, Cal., USA
SO Arthritis Rheum. (38, No. 6, Suppl., R10, 1995)
CODEN: ARHEAW ISSN: 0004-3591
AV UCLA School of Medicine, Los Angeles 90024, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB To evaluate therapeutic potential in collagen-induced arthritis (CIA), rats were administered p.o. thalidomide or either of 2 analogs, EM-12 or supidimide. Suppression of inflammatory synovitis was lower in all experimental groups. The EM-12 analog was the most efficacious and b.i.d. thalidomide was better than once daily. Incidence of arthritis onset was comparable among all groups. Strong cell-mediated and humoral responses to type II collagen (CII) were similar in the experimental and control groups. Results suggest that thalidomide and its analogs may be effective in treating inflammatory synovitis and that these benefits might be related to modulation of TNF-alpha and/or angiogenesis. (conference abstract).